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Bupropion SR for smoking cessation in smokers with cardiovascular disease: a multicentre, randomised study

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KEYWORDS

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Aim To investigate the safety and efficacy of bupropion sustained release (bupropion SR) in promoting abstinence from smoking in subjects with cardiovascular disease (CVD).

Methods Six hundred twenty-nine subjects with CVD who smoked ≥ 10 cigarettes/day were randomised in a double-blind, multicentre study to receive bupropion SR (150 mg twice daily) or placebo for 7 weeks, with a follow-up of 52 weeks. Primary efficacy endpoint: continuous abstinence from smoking from weeks 4 to 7. Secondary endpoints: continuous abstinence (weeks 4–12, 4–26 and 4–52) and weekly point prevalence abstinence. All participants received brief motivational support. Safety was evaluated throughout the study.

Results Continuous smoking abstinence rates from weeks 4 to 7 were significantly higher in subjects receiving bupropion SR compared with placebo (43 vs. 19%, odds ratio [OR]=3.27, 95% confidence interval [CI] 2.24–4.84; $P<0.001$). Continuous abstinence rates from weeks 4 to 26 and 4 to 52 continued to be more than double for bupropion SR compared with placebo (27 vs. 11%; 22 vs. 9%, $P<0.001$). Weekly point prevalence abstinence was significantly higher for participants who received bupropion SR compared with placebo at weeks 3, 7, 26 and 52 ($P<0.001$). In both groups, there were no clinically significant changes in blood pressure and heart rate throughout the treatment phase. Overall, 6% of the participants ($n=36$) discontinued study medication due to an adverse event (bupropion SR, $n=17$; placebo, $n=19$).

Conclusions After 7 weeks of bupropion SR treatment, more than twice as many smokers with CVD had quit smoking at 1 year compared with placebo. The safety profile of bupropion SR was similar to that previously observed in general smoking populations.
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Introduction

Strong, consistent epidemiological evidence links cigarette smoking to increased cardiovascular disease (CVD) morbidity and mortality.^{1,2} In the developed world, CVD (most often ischaemic heart disease) is the most common smoking-related cause of death, with 25% of deaths in the 35–69 years age group being due to tobacco.³ It has been recognised for some time that mortality levels are significantly higher among smokers who have experienced a myocardial infarction and continue to smoke, compared with those who quit.⁴ Furthermore, the risk of a coronary event declines rapidly after stopping smoking, and after 2–3 years of abstinence the risk of such an event is similar to that for subjects who have never smoked.^{5–7} For this reason, the Joint British Recommendations on Prevention of Coronary Heart Disease in Clinical Practice state that stopping smoking is one of the primary lifestyle options for reducing the risk of coronary heart disease.⁸

Bupropion sustained release (bupropion SR) is a non-nicotine-based treatment for use in smoking cessation. Controlled clinical studies involving approximately 8000 subjects receiving bupropion SR have now demonstrated the efficacy and tolerability of this agent.^{9–13} This efficacy is acknowledged in smoking cessation guidelines^{14–16} and the National Institute for Clinical Excellence has recently recommended its use in smoking cessation.¹⁷ Bupropion SR is effective in smokers who may be considered particularly refractory to treatment.^{11,18} In addition, meta-analyses suggest that the efficacy, tolerability and safety of bupropion SR are unaffected by a previous history of serious conditions such as alcoholism and major depression.¹⁹ However, there have been no clinical studies carried out to date that have assessed bupropion SR as an aid to smoking cessation in subjects with CVD. Smokers who have survived a cardiac event but not quit smoking may be more nicotine dependent or face more barriers to quitting than other smokers.

We conducted a double-blind, multicentre, randomised study to assess the efficacy and safety of bupropion SR in subjects with smoking-related CVD.

Methods

Participants

We enrolled adults who smoked an average of ≥ 10 cigarettes/day during the previous 12 months and who had not made a serious attempt to stop

smoking using nicotine replacement therapy during the previous 3 months. Subjects had not made a quit attempt lasting >3 months during the previous year. All participants were motivated to stop smoking and had at least one of the following cardiovascular conditions: myocardial infarction >3 months ago, interventional cardiac procedure (excluding valve replacement) >3 months ago, stable angina pectoris, peripheral vascular disease (excluding varicose veins and current deep vein thrombosis) or congestive heart failure (NYHA Class I or II). Subjects with at least one of these conditions, with or without hypertension, were eligible. However, hypertension had to be controlled (i.e. $<160/100$ mmHg; baseline systolic and diastolic values, respectively) by diet, exercise, or medication.

Subjects were excluded if they had a predisposition for seizure; had a current diagnosis of severe renal, hepatic, haematological, pulmonary or neurological disease; or had a history or current diagnosis of bulimia or anorexia nervosa. Subjects were also excluded if they had an acute or chronic medical condition likely to impair drug absorption, distribution, metabolism or excretion; had a history or current diagnosis of panic disorder, psychosis, or bipolar disorder; or were depressed.

The protocol was approved by the appropriate Independent Ethics Committee or Institutional Review Board and participants provided written informed consent.

Interventions

We performed a multicentre, randomised, double-blind, placebo-controlled study in subjects from 28 centres across 10 countries.

The study consisted of a 1- to 2-week screening/baseline phase, a 7-week treatment phase and follow-up at 3, 6 and 12 months. Subjects set a target quit date for >7 but ≤ 14 days after baseline assessment. At baseline, smoking history and cardiovascular diagnoses were collected, and expiratory carbon monoxide levels were measured using a Bedfont Smokerlyser monitor. Participants were also weighed and two questionnaires (the Fagerström Tolerance Questionnaire^{20,21} and a Smoking Assessment Questionnaire) were completed. Participants were then randomised in a 1:1 ratio to receive either bupropion SR (150 mg/day on days 1–3; 150 mg twice daily on days 4–49) or placebo during the 7-week treatment phase.

Subjects were contacted by telephone 1 day before their target quit date and reminded that they were due to stop smoking the following day. Three days after this date, subjects were again

contacted to provide motivational support. Participants recorded their cigarette consumption (number of cigarettes per day) on a diary card and visited the clinic each week throughout the treatment phase. At each clinic visit, subjects were weighed, vital signs and expiratory carbon monoxide levels measured and brief motivational support (10–15 min) was given. At week 7, the Smoking Assessment Questionnaire was completed.

During follow-up, subjects were contacted at monthly intervals to encourage abstinence from smoking and prevent relapse. At weeks 12, 26 and 52, subjects were weighed, expiratory carbon monoxide levels and vital signs were measured and brief motivational support given. Subjects who withdrew or missed a clinic visit were assumed to be smoking.

Primary outcomes

The primary outcome was defined as continuous abstinence from smoking for a 4-week period from the beginning of week 4 of the treatment phase. Continuous abstinence was assessed by the investigator and confirmed by the subject's self-report of not smoking and an expiratory carbon monoxide level <10 ppm. Subjects with missing investigator assessments were assumed to be smokers at that visit.

Secondary outcomes

Secondary outcomes of efficacy included continuous abstinence from smoking from week 4 to weeks 12, 26 and 52. In addition, weekly point prevalence abstinence (abstinence from smoking for the previous 7-day period) was assessed during the treatment and follow-up phase.

Change in body weight relative to baseline was assessed at the end of the treatment phase (week 7) and at weeks 26 and 52 of the follow-up phase.

At week 7, subjects were asked to evaluate their experience with the study medication, and whether they would recommend it to other smokers (Smoking Assessment Questionnaire).

Safety

Vital signs were recorded throughout the study, and adverse events were recorded throughout the treatment phase and up to week 9. All serious adverse events were collected throughout the treatment phase, after which only serious adverse events related to study medication were recorded.

Statistics

In the study of Tashkin et al.,¹¹ which examined smokers considered refractory to treatment, the

4-week continuous abstinence rate was 15% for subjects receiving placebo. We considered a 10% increase in the continuous abstinence rate for subjects receiving bupropion SR to be clinically relevant. Therefore, we assumed that 15% of subjects receiving placebo and 25% of subjects receiving bupropion SR would remain continuously abstinent during weeks 4–7 of the current study. With 620 participants randomised 1:1, the study would have at least 85% power to detect this difference at the two-sided 5% level of significance and detect a difference assuming that 5% of the subjects randomised to placebo and 12% of those randomised to bupropion SR, remained continuously abstinent at 6 months.

Data were analysed using sas® (v.6.12) statistical software. For continuous abstinence data, comparison of the treatment groups was performed using an exact test according to Gart and Cox^{22,23} stratified by country. For point prevalence abstinence, the treatment groups were compared using the exact test. Change in weight relative to baseline was compared by analysis of covariance including terms for treatment, centre, gender and abstinence status, with baseline weight as a covariate.

Results

Participant characteristics

Six hundred and sixty-nine potential subjects were screened, and 629 participants were enrolled, of whom 626 received at least one dose of study medication (intent-to-treat population; $n=313$ in each group) [Fig. 1]. After 52 weeks, 120 (38%) patients receiving bupropion SR and 155 (50%) receiving placebo had prematurely discontinued treatment.

Treatment groups were comparable in terms of age, gender, race and smoking history (Table 1). This population of chronic smokers had a mean pack-year history of 49.6 years and a mean Fagerström Tolerance Questionnaire score of 6.6. Most subjects (85%) had made at least one previous attempt to stop smoking, and 31% had made ≥ 5 previous cessation attempts. Overall, 27% of subjects had chronic obstructive pulmonary disease and/or diabetes and the incidence of these conditions was similar for both treatment groups (Table 1). Subjects entering the study presented with a range of cardiovascular diagnoses and included 306 (49%) who had previously experienced a myocardial infarction (Fig. 2). Patients must have had at least one of the following to be eligible for the study (\pm controlled hypertension): myocardial

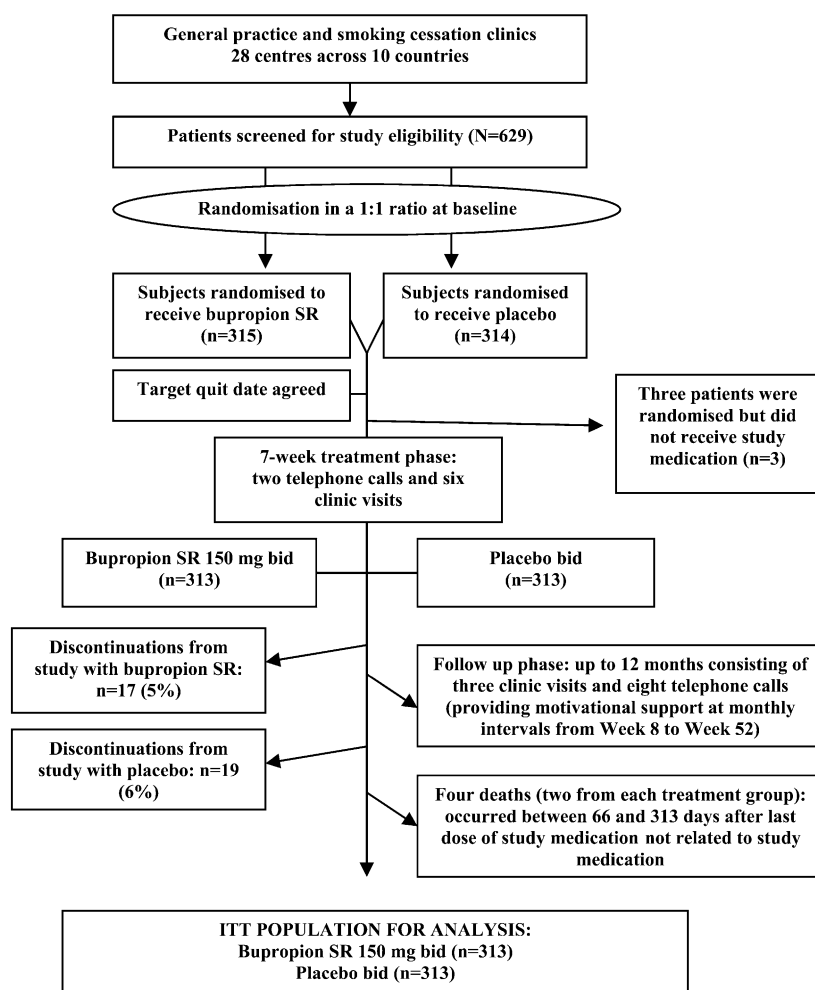


Fig. 1 Participant flow diagram.

infarction (>3 months ago), interventional cardiac procedure (>3 months ago), stable angina, peripheral vascular disease (excluding varicose veins and current deep vein thrombosis) or congestive heart failure (class I or II).

Primary outcomes

A significantly higher percentage of subjects receiving bupropion SR achieved continuous abstinence from smoking for weeks 4–7 (Fig. 3) compared with those receiving placebo—43% (134/313) of subjects receiving bupropion SR remained abstinent, compared with 19% (61/313) of those receiving placebo ($P<0.001$, odds ratio [OR] 3.27; 95% confidence interval [CI] 2.24–4.84).

Secondary outcomes

Bupropion SR treatment resulted in consistently higher rates of abstinence than placebo. At week

26, 27% (84/313) of subjects receiving bupropion SR remained abstinent, compared with 11% (34/313) of those receiving placebo ($P<0.001$). At week 52 the corresponding values were 22% (68/313) and 9% (29/313) for bupropion SR vs. placebo, respectively ($P<0.001$).

In both treatment groups, subjects with CVD and chronic obstructive pulmonary disease and/or diabetes had similar continuous abstinence rates for weeks 4–52 compared with CVD only (18 and 15%, respectively).

Point prevalence abstinence

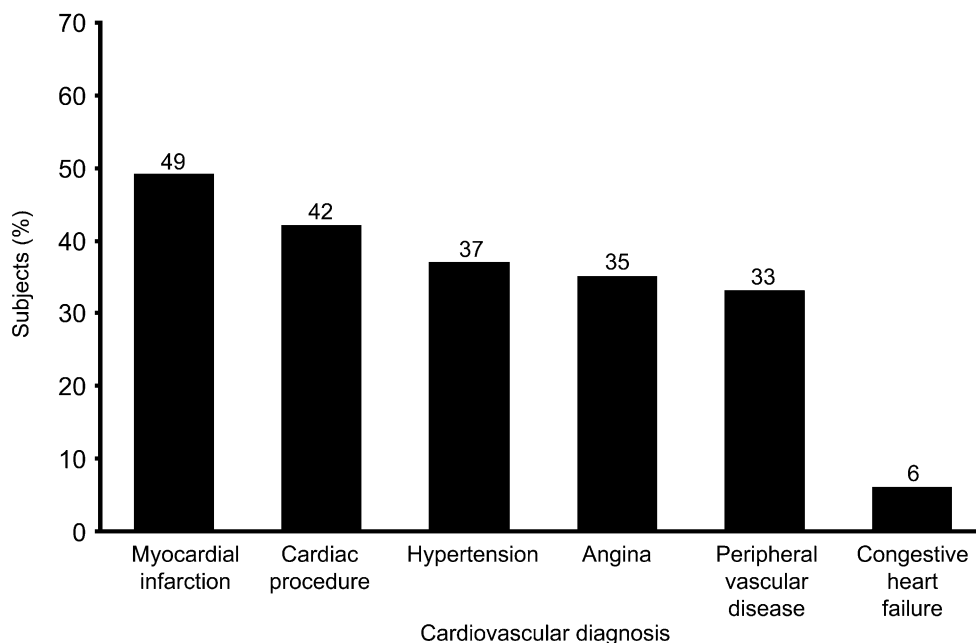
Weekly point prevalence abstinence for the bupropion SR group remained more than double that of the placebo group throughout the study. Statistical analysis revealed significantly greater weekly point prevalence abstinence ($P<0.001$) in participants receiving bupropion SR compared with placebo at all prespecified time points (Fig. 4).

Table 1 Baseline characteristics

	Bupropion SR (n=313)	Placebo (n=313)
Age [mean (SD)]	55.6 (9.2)	55.1 (9.0)
Female	26%	21%
Caucasian	98%	99%
Age started smoking [mean (SD)]	17.1 (4.9)	16.8 (4.3)
Pack years [mean (SD)]	49.8 (27.1)	49.3 (23.7)
Cigarettes per day [mean (SD)]	25.2 (12.2)	25.6 (11.7)
Fagerström Tolerance Questionnaire score [mean (SD)] ^a	6.5 (2.0)	6.6 (2.0)
Quit attempts		
Previous number of attempts [mean (SD)]	6.1 (12.3)	4.7 (8.2)
Used willpower [number of subjects (%)]	221 (71)	208 (66)
Used nicotine replacement therapy [number of subjects (%)]	135 (43)	132 (42)
Comorbid conditions		
Chronic obstructive pulmonary disease [number of subjects (%)]	54 (17)	41 (13)
Diabetes [number of subjects (%)]	44 (14)	43 (14)

Pack year history=([number of years smoking]×[number of cigarettes per day])/20.

^an=263 for bupropion SR and placebo.

**Fig. 2** Cardiovascular diagnoses at baseline for all subjects (n=626).

At weeks 7 and 26 the odds of not having smoked during the preceding week were almost four times higher for bupropion SR-treated subjects compared with those receiving placebo (OR 3.96, 95% CI 2.74–5.79; OR 3.85, 95% CI 2.50–6.03, respectively).

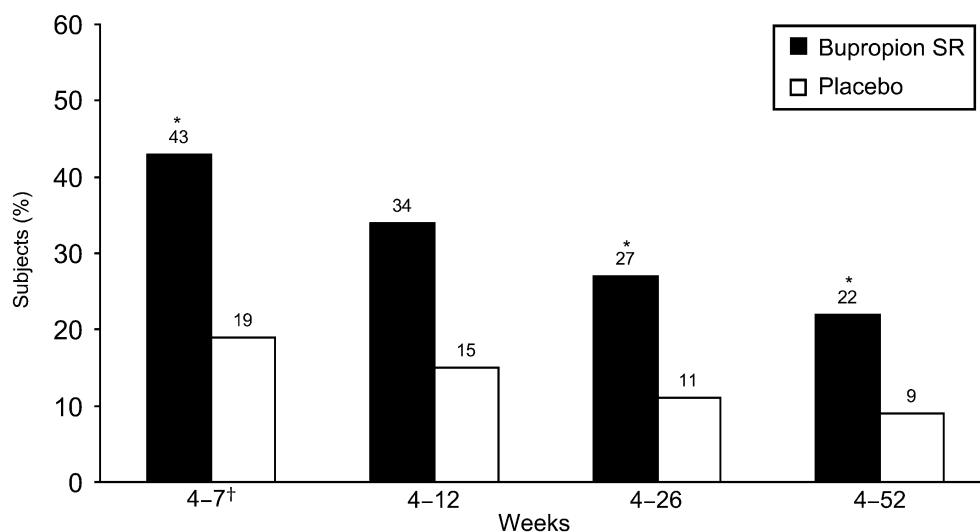
Body weight

During the treatment phase, subjects receiving bupropion SR who had abstained from smoking from the beginning of week 4 to the end of week 7 gained an average of 1.15 kg less weight than those

receiving placebo (95% CI 0.46–1.83 kg). However, participants who remained abstinent at week 52 experienced a similar overall gain in weight, regardless of treatment group, with bupropion SR-treated subjects gaining an average of 0.9 kg more at week 52 (95% CI –1.19 to 2.80 kg).

Smoking assessment questionnaire

Responses to the Smoking Assessment Questionnaire were more positive for bupropion SR than placebo in four of the seven questions (Fig. 5). At



Statistical analysis performed only at weeks 7, 26 and 52

Weeks 4-7: OR 3.27; 95% CI 2.24-4.84

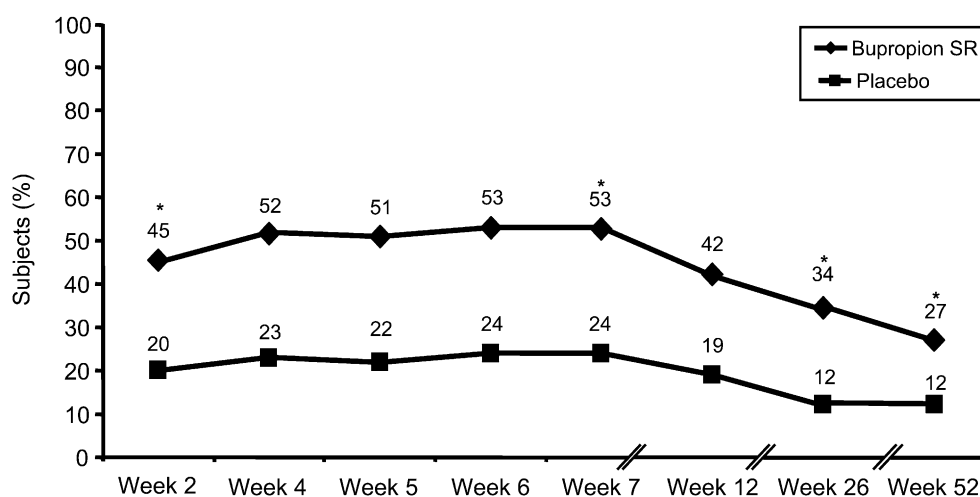
Weeks 4-26: OR 3.09; 95% CI 1.96-4.96

Weeks 4-52: OR 2.78; 95% CI 1.70-4.63

*P<0.001

†Primary efficacy endpoint

Fig. 3 Continuous abstinence during the treatment and follow-up phases.



Statistical analyses performed only at weeks 3, 7, 26 and 52

Week 3: OR 3.31, 95% CI 2.28-4.84

Week 7: OR 3.96, 95% CI 2.74-5.79

Week 26: OR 3.85, 95% CI 2.50-6.03

Week 52: OR 2.87, 95% CI 1.83-4.57

*P<0.001

Fig. 4 Weekly point prevalence abstinence during the treatment and follow-up phases.

the end of treatment, 61% of subjects in the bupropion SR group considered that the urge to smoke was not a problem, compared with 37% of those receiving placebo. Both treatment groups generally felt that side effects were not a problem. However, 28% of subjects receiving bupropion SR

felt that altered sleeping patterns were a problem compared with 16% for placebo.

In total, 89% of subjects in the bupropion SR group stated that they would recommend their study medication to other smokers, compared with 72% of those in the placebo group.

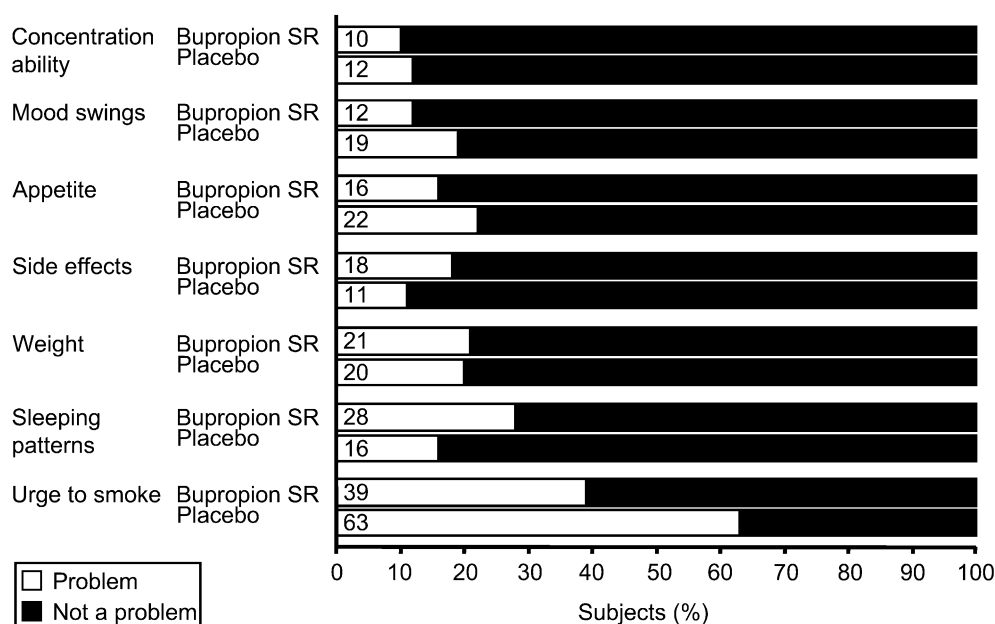


Fig. 5 Smoking Assessment Questionnaire responses at the end of treatment.

Table 2 Summary of adverse events

	Bupropion SR (n=313)	Placebo (n=313)
Adverse event		
Insomnia	75 (24)	37 (12)
Dry mouth	55 (18)	31 (10)
Nausea	40 (13)	19 (6)
Headache	35 (11)	34 (11)
Dizziness	24 (8)	17 (5)
Constipation	16 (5)	4 (1)
Sweating	16 (5)	10 (3)
Insomnia	4 (1)	1 (<1)
Nausea	5 (2)	3 (<1)
Headache	3 (<1)	4 (1)
Dizziness	2 (<1)	3 (<1)
Abdominal pain	1 (<1)	3 (<1)

Safety

A total of 64% (201/313) of subjects receiving bupropion SR and 58% (181/313) of those receiving placebo experienced at least one adverse event whilst on treatment (and 2 weeks thereafter). The most frequently reported events were insomnia (24% bupropion SR; 12% placebo) and dry mouth (18% bupropion SR; 10% placebo) [Table 2]. The frequency with which these events were reported was similar regardless of disease group (CVD or CVD and chronic obstructive pulmonary disease and/or diabetes) or age.

In total, 38 subjects (6%) reported cardiovascular adverse events (bupropion SR $n=24$; placebo $n=14$). The most common were angina pectoris (bupropion SR $n=7$; placebo $n=4$), hypertension (bupropion SR $n=2$; placebo $n=3$), and palpitations (bupropion SR $n=4$; placebo $n=1$).

A total of 36 participants (6%) discontinued from the study due to an adverse event (bupropion SR $n=17$ [5%]; placebo $n=19$ [6%]) (Table 2). Eight participants experienced a total of nine serious adverse events during the study, and five of these occurred during treatment (bupropion SR $n=5$, placebo $n=0$). Three events were considered to be possibly a worsening of a preexisting condition, angina pectoris ($n=2$) and vascular disease ($n=1$). Glaucoma ($n=1$) and lupus erythematosus disseminatus ($n=1$) were also reported. Only one of these events was considered possibly related to study treatment (lupus), and none led to discontinuation of study medication. One event (worsening of congestive heart failure) occurred following the screening visit, prior to the receipt of study medication, in a patient ultimately randomised to placebo.

Within a week of finishing treatment, three serious adverse events were reported. One subject had received bupropion SR during the treatment phase, and the event (vestibular disorder) was not considered to be related to study medication. The two remaining events (chest pain, dyspnoea) were reported by one subject who had received placebo.

There were four deaths during the study (two patients receiving bupropion SR and two receiving placebo), and none was related to study medication. All deaths occurred during the follow-up phase and occurred between 66 and 313 days after the last dose of study medication.

Vital signs

No overall treatment effect was observed in systolic and diastolic blood pressure and heart rate (mean changes in beats per minute from baseline to week 7 were -2.15 and -0.80 , for bupropion SR and placebo, respectively). No clinically significant change in vital signs was seen for either treatment during the follow-up phase to week 52. At week 52, the mean change from baseline in systolic blood pressure with bupropion SR and placebo was $+1.5$ and $+3.5$ mmHg, respectively. The corresponding change from baseline in diastolic blood pressure with bupropion SR was $+0.7$ mmHg compared with $+2.2$ mmHg for placebo.

Discussion

We have conducted the first prospective study of non-nicotine pharmacotherapy in a population of persistent smokers with CVD, nearly half of whom had experienced a myocardial infarction >3 months previously. At 6 and 12 months after beginning treatment, subjects who had received bupropion SR were significantly more likely to have successfully stopped smoking than those receiving placebo. Bupropion SR was well tolerated and the safety profile was more favourable than expected for a study population of this type.

Smokers in the present study were recruited in the settings of primary and secondary/tertiary care in addition to smoking cessation clinics. Thus, these smokers were clearly different from smokers recruited to previous studies of bupropion SR conducted in subjects recruited from a general smoking population, with the exception of one study carried out in patients with chronic obstructive pulmonary disease.¹¹ All patients were diagnosed with a cardiovascular condition, over one-quarter were also diagnosed with chronic obstructive pulmonary disease and/or diabetes, and most (96%) were taking concomitant medications. Furthermore, the mean pack year history (49.6 years) and mean number of quit attempts (5.4) were higher than observed in previous bupropion SR studies in general smoking populations.^{9,10} However, this smoking profile was similar to that of subjects with chronic obstructive pulmonary disease recruited in

a more recent bupropion SR study¹¹ in that both of these populations were older, less healthy, had smoked for a longer period of time and made more quit attempts than participants in earlier studies.^{9,10} In addition, both study populations comprised subjects with chronic smoking histories who continued the habit despite developing smoking-related diseases, and who may therefore be particularly refractory to smoking-cessation treatment.

Bupropion SR was significantly more effective than placebo as an aid to smoking cessation for smokers with CVD and the odds of being continuously abstinent by week 4 and maintaining this until weeks 26 and 52, were around three times greater for bupropion SR. Weekly point prevalence analysis (continuous abstinence 7 days prior to each clinic visit) confirmed these findings, with rates being more than double throughout the study for bupropion SR compared with placebo. Notably, abstinence rates were comparable to those found in previous clinical studies in a general smoking population^{9,10,12} and to that estimated in a recent meta-analysis conducted by the National Institute for Clinical Excellence. This meta-analysis reported that treatment with bupropion gave an OR of 2.16 (95% CI 1.51–3.10) for continuous abstinence compared to placebo.¹⁷ The institute estimated that nicotine replacement therapy gave an OR of 1.69 (95% CI 1.57–1.82) compared to placebo.¹⁷

The motivational support provided during this study was minimal (10–15 min sessions with existing clinical staff) and similar to that provided in previous trials of bupropion SR. Furthermore, the weight gain in subjects treated with bupropion SR was noticeably less than that in the placebo group while they were receiving treatment. This finding is significant because individuals often start smoking again if they gain weight,²⁴ and although the benefit appears to be short term, bupropion SR may help to alleviate this.

Responses to the Smoking Assessment Questionnaire add further support to these central efficacy findings. More than half of subjects confirmed that the urge to smoke was not a problem with bupropion SR, and the majority stated they would recommend their treatment to others. This is in line with findings from a previous study in 91 chronic smokers, where bupropion SR was found to ameliorate selected nicotine withdrawal effects (difficulty in concentrating, irritability and depression).²⁵

We hypothesised that as the current study examined persistent smokers with serious disease,

there may be an increase in the rate of adverse events and in vital sign abnormalities (particularly blood pressure and pulse rate) compared with previous studies of general smoking populations. However, bupropion SR was well tolerated with a safety profile comparable to that seen previously and with few discontinuations due to adverse events. Importantly, although bupropion is a norepinephrine reuptake inhibitor its administration had no impact on vital signs such as blood pressure. There were no cases of seizure or severe hypersensitivity reactions in this study. Each of these adverse events has previously been reported to occur in about 0.1% of subjects treated with bupropion SR,^{26,27} thus, less than one case of each would be expected in the current study.

In this study we have shown that treatment with bupropion SR can significantly improve rates of smoking abstinence over placebo in a population of smokers with stable CVD who had previously been recalcitrant to quitting. The safety profile and positive patient responses further suggest that bupropion SR is a valuable medication for smoking cessation in smokers with CVD.

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References

1. Parish S, Collins R, Peto R et al. Cigarette smoking, tar yields, and non-fatal myocardial infarction: 14,000 cases and 32,000 controls in the United Kingdom. The International Studies of Infarct Survival (ISIS) Collaborators. *BMJ* 1995;311:471–7.
2. McGinnis JM, Foege WH. Actual causes of death in the United States. *J Am Med Assoc* 1993;270:2207–12.
3. The World Health Organization. The World Health Report; 1999.
4. Daly LE, Mulcahy R, Graham IM et al. Long term effect on mortality of stopping smoking after unstable angina and myocardial infarction. *Br Med J (Clin Res Ed)* 1983;287:324–6.
5. Rosenberg L, Kaufman DW, Helmrigh SP et al. The risk of myocardial infarction after quitting smoking in men under 55 years of age. *N Engl J Med* 1985;313:1511–4.
6. Rosenberg L, Palmer JR, Shapiro S. Decline in the risk of myocardial infarction among women who stop smoking. *N Engl J Med* 1990;322:213–7.
7. Dobson AJ, Alexander HM, Heller RF et al. How soon after quitting smoking does risk of heart attack decline? *J Clin Epidemiol* 1991;44:1247–53.
8. Joint British recommendations on prevention of coronary heart disease in clinical practice. British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society, endorsed by the British Diabetic Association. *Heart* 1998;80(Suppl 2):1–29.
9. Hurt RD, Sachs DP, Glover ED et al. A comparison of sustained-release bupropion and placebo for smoking cessation. *N Engl J Med* 1997;337:1195–202.
10. Jorenby DE, Leischow SJ, Nides MA et al. A controlled clinical trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med* 1999;340:685–91.
11. Tashkin D, Kanner R, Bailey W et al. Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. *Lancet* 2001;357:1571–5.
12. Tonstad S, Aaserud E, Hjalmarson A et al. on behalf of the Zyban Study Group. Bupropion SR is an effective and well-tolerated aid to smoking cessation in a general smoking population: an international study (ZYB40017). Poster presentation at SRNT Third European Conference; 2001, Sept 20–22; Paris, France.
13. Hays JT, Hurt RD, Rigotti NA et al. Sustained-release bupropion for pharmacologic relapse prevention after smoking cessation: a randomised controlled trial. *Ann Intern Med* 2001;135:423–33.
14. West R, McNeill A, Raw M. Smoking cessation guidelines for health professionals: an update. *Thorax* 2000;55:987–99.
15. Fiore MC. US public health service clinical practice guideline: treating tobacco use and dependence. *Respir Care* 2000;45:1200–62.
16. Lancaster T, Stead L, Silagy C et al. Effectiveness of interventions to help people stop smoking: findings from the Cochrane Library. *BMJ* 2000;321:355–8.
17. Guidance on the use of nicotine replacement therapy (NRT) and bupropion for smoking cessation. Technology appraisal guidance—no. 39. London: National Institute for Clinical Excellence; March 2002.
18. Smoking withdrawal in hospital patients: factors associated with outcome. Subcommittee of the Research Committee of the British Thoracic Society. *Thorax* 1984;39:651–6.

19. Hayford KE, Patten CA, Rummans TA et al. Efficacy of bupropion for smoking cessation in smokers with a former history of major depression or alcoholism. *Br J Psychiatry* 1999;**174**:173–8.
20. Heatherton TF, Kozlowski LT, Frecker RC et al. The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. *Br J Addict* 1991; **86**:1119–27.
21. Fagerström KO, Heatherton TF, Kozlowski LT. Nicotine addiction and its assessment. *Ear Nose Throat J* 1990; **69**:763–8.
22. Gart J. Point and interval estimation of the common odds ratio in the combination of 2×2 tables with fixed marginals. *Biometrika* 1970;**57**:471–5.
23. Cox DR. A simple example of a comparison involving quantal data. *Biometrika* 1966;**53**:215–20.
24. Jeffery RW, Hennrikus DJ, Lando HA et al. Reconciling conflicting findings regarding postcessation weight concerns and success in smoking cessation. *Health Psychol* 2000; **19**:242–6.
25. Shiffman S, Johnstone JA, Khayrallah M et al. The effect of bupropion on nicotine craving and withdrawal. *Psychopharmacology* 2000;**148**:33–40.
26. Dunner DL, Zisook S, Billow AA et al. A prospective safety surveillance study for bupropion sustained-release in the treatment of depression. *J Clin Psychiatry* 1998;**59**: 366–73.
27. Ferry L, Johnston A. Efficacy and safety of bupropion SR for smoking cessation: data from clinical trials and 5 years of postmarketing experience. 3rd European Congress on Tobacco or Health; 2002 June 19–22; Warsaw, Poland.